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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,327	04/20/2001	Nathaniel A. Brown	PU3514USW	9628

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EXAMINER	
JIANG, SHAOJIA A	
ART UNIT	**PAPER NUMBER**
1617	16

DATE MAILED: 06/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/787,327	Applicant(s) BROWN ET AL.	
	Examiner Shaojia A. Jiang	Art Unit 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-10,12-15,22 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-10,12-15,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 8, 2003 has been entered in Paper No. 14.

This Office Action is a response to Applicant's request for continued examination (RCE) filed April 8, 2003 in Paper No. 14, and response to the Final Office Action (mailed November 29, 2002), filed April 8, 2003 in Paper No. 15 wherein no claims are amended or added. Currently, claims 1-2, 4-10, 12-15, and 22-23 are pending in this application.

Claims 1-2, 4-10, 12-15, and 22-23 are examined on the merits herein.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 4-10, 12-15, and 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shaw et al. (CF, PTO-1449 submitted March 21, 2001) and Korba (of record) in view of Glazier et al. (5,627,165, of record).

Shaw et al. discloses that a combination of lamivudine (3TC) and PMEA exhibits a synergistic inhibition of HBV. Shaw et al. also discloses the effective amount of PMEA (0.15/5 μM =) 0.03 μM, since it reduced 5 fold in the presence of 0.05 μM 3TC in the combination to be administered simultaneously (see the abstract). Hence, the ratio of 3TC to PEMA is 1.67, within the instant claimed range.

Korba teaches lamivudine is useful in methods of treatment of HBV infections. Korba also teaches that lamivudine in combination with other antiviral agents such as penciclovir which is known antiviral agent against HBV is useful in a pharmaceutical composition or formulation for oral administration and methods of treatment of HBV infections, exhibiting synergistic effect. See abstract, the right column of page 49, the 3rd and 4th paragraphs of page 50.

The prior art does also not expressly disclose a pharmaceutical composition or formulation comprising lamivudine (3TC) and adefovir dipivoxil, the prodrug of PEMA in unit dosage form and the particular ratio of lamivudine (3TC) and the prodrug of PEMA herein, the manner of administration of the pharmaceutical composition or formulation herein.

Glazier et al. discloses that adefovir (PMEA) or adefovir dipivoxil (Bis(pivaloyloxymethyl)PMEA, the prodrug of PMEA herein) is known to be useful in a pharmaceutical composition or formulation and methods of treatment of HBV infections.

Glazier et al. also discloses that the prodrug of PMEA herein enhances intracellular PMEA delivery and have enhanced antiviral activity (see particularly col.1 lines 66 to col.2 line 2, col.3-6). See also col.34 lines 39-40, col.37 lines 5-19, col.38 Tables, and claims 1-38.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ lamivudine in combination with adefovir dipivoxil, the prodrug of PMEA herein, in a pharmaceutical composition or formulation and methods of treatment of HBV infections, and to determine the manner of administration of the pharmaceutical composition or formulation herein and to optimize the effective amounts of active agents in the composition herein to be administered.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ lamivudine in combination with adefovir dipivoxil, the prodrug of PMEA herein, in a pharmaceutical composition or formulation and methods of treatment of HBV infections, since the combination of lamivudine (3TC) and PMEA (adefovir) is known to be useful in a pharmaceutical composition or formulation and in methods of treatment HBV infections because the combination of lamivudine (3TC) and adefovir is know to exhibit synergistic effects against HBV according to Shaw et al. Moreover, adefovir dipivoxil, the prodrug of PMEA herein is known to better than the parent drug, PMEA, since the prodrug of PMEA herein is known to enhance intracellular PMEA delivery and have enhanced antiviral activity according Glazier et al. Therefore, one of ordinary skill in the art would have found it obvious to employ the prodrug of PMEA in combination with lamivudine (3TC) based on the prior art teachings. Hence,

the disclosure of Shaw et al. has clearly provided the motivation of making the combination herein in view of Glazier et al.

Further, one of ordinary skill in the art would have reasonably expected that combining lamivudine and adefovir or adefovir dipivoxil known useful for the same purpose in a composition to be administered would improve the therapeutic effect for treating HBV infections.

Since all composition components herein are known, it is considered prima facie obvious to combine them into a single composition useful for the very same purpose. At least additive therapeutic effects would have been reasonably expected. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980).

Additionally, one of ordinary skill in the art would have been motivated to determine the manner of administration of the composition herein and to optimize the effective amounts of active ingredients in the composition because the determination of the manner of administration and the optimization of amounts of active agents to be administered is considered well within the skill of artisan. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients and the manner of administration, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Applicant's remarks filed on April 8, 2003 in Paper No. 15 with respect to the rejection of claims 1-2, 4-10, 12-15, and 22-23 made under 35 U.S.C. 103(a) as being

unpatentable over Korba and Glazier et al. (5,627,165) of record in the previous Office Action November 29, 2002 have been considered but are moot in view of the new ground(s) of rejection above.

Additionally, Applicant's assertion that Figure 1 of the specification demonstrates the claimed combination herein shows unexpected and synergistic activity against HBV production has been considered but is not found convincing since the synergistic results in the testing of the combination of lamivudine and PMEA (adefovir) shown in Figure 1 in the specification is clearly taught and suggested by Shaw et al. Therefore, the results herein are clearly expected and not unexpected based on the cited prior art. It is noted that the combination tested herein is not the combination of lamivudine and the prodrug of PMEA, adefovir dipivoxil. Nonetheless, the combination of lamivudine and adefovir dipivoxil (the prodrug of PMEA) would be also expected to show synergistic effects against HBV based on the prior art. Expected beneficial results are evidence of obviousness. See MPEP § 716.02(c).

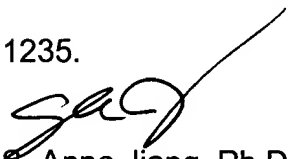
Therefore, the evidence presented in the specification herein is not seen to support the nonobviousness of the instant claimed invention over the prior art.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (703) 305-1008. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (703) 305-1877. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-1235.



S. Anna Jiang, Ph.D.
Patent Examiner, AU 1617
June 3, 2003